Endpoints in Alzheimer’s Disease Clinical Trials
Fundamentals and Potential Paths

ISCTM Annual Meeting
Alzheimer’s Disease Working Group
Washington, DC    February 2016

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The views expressed are those of the author, and do not necessarily represent a Janssen position
Outline

• Fundamentals of Endpoints and Assessments
• Efficacy – Treatment Benefit
• Assessment Interpretability
• Endpoint Perspectives for Early Alzheimer’s Disease Studies
• Endpoint:

- Specific assessment(s) used as study outcome (OA)
- At specific time(s),
- Analyzed by a specific statistical method
- The assessment in isolation is not a study endpoint
- Endpoint meaning – Interpretation
  - Biological activity of the treatment
  - Clinical efficacy of the treatment
- Both the interpretability and the statistical properties of the endpoint affected by all the selected specifics
Outcome Assessments

• Biomarker
  ➢ Intrinsic property of the patient

• Clinical Outcome Assessment (COA)
  ➢ Does not ‘exist’ without:
    ❖ Human judgment – Evaluator or patient and/or
    ❖ Active participation by patient
  ➢ Categories: ClinRO, PRO, ObsRO, PerfO
  ➢ Defined method to measure a “Concept of Interest” (COI)

• Intended interpretation – activity or efficacy

Endpoint Use in Drug Development

• Provide proof of concept evidence
• Guide stepwise development decisions
• **Basis for marketing approval and labeling claims**
  ➢ Based on showing a specific treatment benefit
• Selected to suit endpoint’s objective
  ➢ Interim analysis of study data for adaptive design
  ➢ Final analysis for study’s overall objective
• Selected endpoint interacts with other design features, e.g., study population, sample size, duration
Efficacy: Treatment Benefit

• A favorable *and meaningful* effect on an aspect of a patient’s life

• How a patient feels, functions, or survives
  ➢ Survival evaluation well established methods
  ➢ Feels and Functions are more complex

• Demonstrated by an endpoint
  ➢ Observed effect on the OA can be reliably interpreted as a **treatment benefit**
  ➢ Interpretation includes consideration of the size of the actual observed effect
Feels and Functions as Effectiveness

• Feels
  ➢ A patient’s physical sensation or perceived mental state related to health *within typical ‘daily’ life*
  ➢ Pain
  ➢ Severely low mood (depression)
  ➢ Not the fundamental physical sensory abilities

• Functions
  ➢ A patient’s ability to perform an activity that is a meaningful part of typical ‘daily’ life
  ➢ Not isolated physiologic processes (eg liver metabolic function) or fundamental motor function
  ➢ Not ability to perform actions not part of usual life

• Generally a complex integrated result of multiple basic biological systems
Interpretability of Efficacy Outcomes

• Do differences or changes in the measurement mean something?
  ➢ *To the patient*
  ➢ Efficacy OAs are intended to inform regarding some specific conceptualized meaningful aspect of patient’s life

• Why Interpretable?
  ➢ Interpretability for meaning allows **benefit-risk assessment** to be formed

• Clinically significant is not identical to statistically significant
  ➢ Meaningfulness of change vs Sensitivity to change
COA Relationships

Meaningful Feeling, Function, or Survival (Meaningful Aspect of Health)

Concept of Interest to be measured

Specific Feelings or Activities that occur in a person’s typical life

Specific Outcome Assessment

COA
COA Relationships

Comprehensive Meaningful Functions affected by disease

Ambulation Dependant Function (Activities)

Walking in shopping mall
Walking from bus stop to office or home
Walking from building to building along a street
Walking from room to room inside house

Arm & Hand Dependant Activities

Cognitive Function Dependant Activities

Walking speed

Leg muscle strength

Walking capacity

Maximal isometric quadriceps force

6 Min walk test

Timed 25 ft walk

Concepts of Interest for measurement (COI)

Meaningful Aspects of Health

Specific Meaningful Activities
Interpretability: Direct and Indirect

• Direct COAs
  ➢ Generally clear what a difference means to a patient in a ‘typical’ daily life

• Indirect COAs
  ➢ Meaning to patient of a difference not intrinsically clear
  ➢ Establishing meaning may be difficult, but is important
  ➢ “Indirectness” is a graded characteristic

• Indirect OAs often selected over direct OAs
COA Interpretability

**Direct COA**
(Direct measures of feeling, function or survival)

- Brief Pain Inventory
- McGill Pain Questionnaire
- St. George Respiratory Questionnaire
- Beck Depression Inventory
- Epworth Sleepiness Scale

**Mildly Indirect COA**

- 6-Minute Walk Test
- PANSS
- ALS Functional Rating Scale
- Sleep onset (time to)
- Visual acuity – ETDRS Scale
- BPRS (brief psych rating)
- Psoriasis Area and Severity Index
- Montgomery-Asberg Depression Rating Scale
- Rankin Stroke scale
- Pulmonary Function Test (FVC, FEV1)
- Ashworth Spasticity Scale
- ADAS-COG
- SDMT

**Very Indirect COA**

- Serum Cholesterol
- HIV Viral Load
- Phenylalanine
- XRay Feature
- HgbA1c
- Hgb
- MRI Brain Lesion Volume

**Biomarkers: Highly Indirect Outcomes Assessments**

- Serum Cholesterol
- HIV Viral Load
- Phenylalanine
- XRay Feature
- HgbA1c
- Hgb
- MRI Brain Lesion Volume
Difficult Early Alzheimer’s Disease Drug Development – Endpoint Aspects

• Need for Activity outcome assessment
  ➢ POC, dose selection, population selection, etc

• Need for efficacy outcome assessment
  ➢ Sensitive to changes of this stage in feasible time frame

• Currently known assessments sub-optimal

• Large, Long, Expensive clinical trials
  ➢ No known pharmacodynamic endpoints to support stand alone short, small size POC or dose selection beyond immediate biochemical effects
  ➢ No known sensitive, interpretable, efficacy assessment

• New assessments –
  ➢ May have better properties
  ➢ Will take time and resources to develop
Thoughts on Drug Activity Assessments in Early AD

• Histological proxies
  - Unclear, and probably limited sensitivity
  - Unclear relationship to brain function
    - Shape, location of relationship

• Biochemical measurements
  - CSF not easily measured frequently
  - Blood at least one step further distant
  - Unclear relationship to brain function

• Neural pathway function
  - Evaluation of simplified function
    - Especially if near maximal stress of pathway function
  - Examines actual brain function status
  - Might be COA or biomarker
  - ? Potential value?
Neural Pathway Actions: Study Activity Assessment?

- N= 20 – 30 per group
- Yang, et.al. Specific Saccade Deficits in Patients with AD at Mild to Moderate Stage and in Patients with Amnestic MCI Age-2013

Fig. 2  Group mean latency of saccades with standard error for leftward, rightward, upward, and downward saccades in healthy elderly, MCI, and AD in conditions gap (a) and overlap (b, c); asterisks indicate significant difference (p<0.05)
Neural Pathway Actions: Study Activity Assessment?

- N = 20 / group. Also seen with word length
Neural Pathway Actions: Study Activity Assessment?

Thoughts on Drug Efficacy Assessments in Early AD

• Traditional measures developed with focus on mild to moderate dementia stage
• Disease manifestations in early stages more nuanced
• May require more complex function measures to detect, measure changes in early AD
  ➢ Greater requirement for efficient integration of multiple aspects of brain activities
  ➢ Possibly in-clinic performance assessments simulating ‘daily life’ activities
  ➢ ? Potential value ?
Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney Memory and Ageing Study

S. Reppermund¹*, H. Brodaty¹,²,³, J. D. Crawford¹, N. A. Kochan¹,⁴, B. Draper¹,³, M. J. Slavin¹,², J. N. Trollor¹,⁵ and P. S. Sachdev¹,²,⁴

Can Performance on Daily Activities Discriminate Between Older Adults with Normal Cognitive Function and Those with Mild Cognitive Impairment?

Juleen Rodakowski, OTD, OTR/L, * Elizabeth R. Skidmore, PhD, OTR/L, * Charles F. Reynolds, III, MD, † Mary Amanda Dew, PhD, † Meryl A. Butters, PhD, † Margo B. Holm, PhD, OTR/L, * Oscar L. Lopez, MD, † and Joan C. Rogers, PhD, OTR/L *  

Complex Functional Measures: Efficacy Assessment?

Outcome Measures
The PASS is a performance-based, criterion-referenced, observational tool designed to examine functional status and change (Rogers et al., 2001). It consists of 26 core tasks, 14 of which are IADL tasks with a cognitive focus and were chosen for this study:
1. Obtaining critical information from visual media (reading a mock newspaper article and answering questions)
2. Obtaining critical information from audio media (listening to a tape recording that simulates radio or television announcements and answering questions)
3. Performing home repairs (identifying why a flashlight does not work and problem solving that the battery is dead)
4. Playing bingo
5. Paying two bills by check (using bill statements to write out checks accurately)
6. Balancing a checkbook ledger (adding a deposit and subtracting the two paid bills)
7. Mailing bills (addressing the envelopes and applying stamps)
8. Using a land line telephone (locating a number for a pharmacy in a phone book, dialing the number, and gathering information from the pharmacy about open hours)
9. Managing medication (sorting medications by time of delivery)
10. Shopping (purchasing precise items on a grocery list using real money)
11. Ascertaining home safety (visually finding safety errors such as a crumpled rug on the floor and problem solving how to fix them)
12. Using a stove (preparing a can of soup)
13. Using an oven (baking muffins)
14. Using sharps (cutting an apple into eight pieces).

The PASS instrument is administered by

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<th>Table 2. Scores on the Performance Assessment of Self-Care Skills Cognitive IADL Tasks, by Group</th>
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<tr>
<td><strong>Control Group (n = 5)</strong></td>
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<tr>
<td><strong>Median (25th, 75th Percentile)</strong></td>
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<tr>
<td><strong>Task</strong></td>
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<td>Total score</td>
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